REMARKS

The application has been amended. Claims 84, 86-90, 93, 95, 97, 98, 99 and 101 have been amended, and claims 91 and 102 have been canceled. The specification has been amended to correct an obvious typographical error in the paragraph spanning lines 16-30 on p. 12 of the application. The amended paragraph corresponds to paragraph [0032] of Applicant's published U.S. Application (Pub. No.: U.S. 2006/0160158A1). Support for this amendment to the specification can be found, for example, in paragraph [0030] of Applicant's published U.S. Application, and in FIG. 1 as filed.

Independent claims 84 and 93 have been amended to recite that the bacterial RNAP homologous secondary channel amino acid sequence to which the agent binds corresponds to, and is alignable with amino acid residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia Coli*. Support for this language can be found, for example, in paragraphs [0027], [0029], [0031], [0036], [0037] and [0094] of Applicant's published U.S. Application.

Claims 87, 88, 97 and 98 have been amended in order to clarify that the "second entity" contains a bacterial RNAP homologous secondary channel amino acid sequence having at least one substitution, insertion, or deletion of amino acid residues corresponding to, and alignable with amino acid residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia Coli*, support for which can be found, for example, in paragraphs [0038], [0039] and [0094] of Applicant's published U.S. Application.

Claims 86, 89, 95 and 99 have been amended in order to clarify that the RNAP derivatives contain a bacterial RNAP homologous secondary channel amino acid sequence having at least one substitution, insertion, or deletion of amino acid residues corresponding to,

and alignable with amino acid residues 736-747 and 779-781 of the β' subunit of RNAP of *Escherichia Coli* or 740-751 and 783-785 of *Bacillius subtilis* RNAP, respectively. Support for these amendments can be found, for example, in paragraphs [0038]-[0039] of Applicant's published U.S. Application.

Claims 90 and 101 have been amended to remove the "derivative" language, and to recite a human RNAP selected from human RNAP I, human RNAP II and human RNAP III, support for which can be found, for example, in paragraph [0030] of Applicant's published U.S. Application and in FIG. 1, as filed. As described in the amended paragraph corresponding to paragraph [0032] of Applicant's published U.S. Application, agents found to bind to the homologous bacterial RNAP homologous secondary channel amino acid sequence in a bacterial RNAP can be analyzed for binding and inhibition of eukaryotic RNAP I, RNAP II and RNAP III. An agent that binds in a target-dependent fashion to the homologous bacterial RNAP homologous secondary channel amino acid sequence in a bacterial RNAP, would not be expected to bind, or would be expected to bind substantially less well to eukaryotic RNAP, including human RNAP I, RNAP II and RNAP III because the target site differs radically in amino acid sequence between bacterial RNAP and eukaryotic RNAP (*see*, for e.g., paragraph [0030] of Applicant's published U.S. Application and FIG. 1).

Claim Rejections Under 35 U.S.C. §112, First Paragraph-Written Description

The Examiner has rejected claims 84-103 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner acknowledges that the specification has sufficient written description of the RNAP secondary channel. However, the Examiner is of the opinion that the specification does not provide sufficient written description of "derivatives of bacterial RNAP secondary channel" and "derivatives of eukaryotic RNAP" needed to practice the claimed invention.

These rejections have been addressed in the amendments presented herewith. With respect to bacterial RNAP derivatives, Applicants have amended the claims in order to clarify that these derivatives contain a bacterial RNAP homologous secondary channel amino acid sequence having at least one substitution, insertion, or deletion of amino acid residues corresponding to, and alignable with amino acid residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia Coli* or 740-751 and 783-785 of *Bacillius subtilis* RNAP. Support for this language can be found, for example, in paragraphs [0038] and [0039] of Applicant's published U.S. Application.

Examples of amino acid substitutions which mapped to the target region specifically set forth in the claims are included in Tables 2 and 5. Therefore, contrary to the Examiner's assertions, there is disclosure of the structure of bacterial RNAP derivatives.

Moreover, contrary to the Examiner's assertions, there is disclosure of the activity of these bacterial RNAP derivatives, as well as disclosure of suitable methods to analyze the activity of the derivatives and disclosure of the identifying characteristics for recognizing that an agent will inhibit the activity of an RNAP derivative. For example, the derivatives were analyzed for their level of MccJ25 resistance Minimum–bacteriocidal-concentration (MBC) assays, as well as by Complementation assays (see Tables 2 and 5, for example), and these methods are described under the "Experimental Procedures" section of Example 1. Assays for antibacterial activity, such as, for example, the disclosed MBC assay, clearly provide an identifying characteristic (i.e, viable cell count) as a means of assessing whether an agent will inhibit the activity of the RNAP derivatives.

With respect to derivatives of eukaryotic RNAP, Applicants have amended the claims to remove the "derivative" language and to recite human RNAP I, human RNAP II and human RNAP III. The structures of human RNAP I, II and III are well known in the art. Moreover, FIG. 1 shows a partial amino acid sequence of human RNAP I, II and II relevant to the present invention. Therefore, there is disclosure of the structure of these human RNAPs. In particular, FIG. 1 shows that the target differs radically in amino acid sequence between bacterial RNAP and eukaryotic RNAP, such as human RNAP. This allows for the identification of molecules that bind, in a target-dependent fashion, to bacterial RNAP, but that do not bind, or that bind substantially less well, to eukaryotic RNAP, including human RNAP I, II and III (paragraph [0030] of Applicant's published U.S. Application).

As described in further detail above, "hits" can be analyzed for binding and inhibition of eukaryotic RNAPs, including human RNAP I, II and III. One of ordinary skill in the art would immediately recognize that the same assays disclosed as being useful to analyze binding and inhibition of bacterial RNAP (test protein) and bacterial RNAP derivatives (control proteins) can be used to analyze for binding and inhibition of human RNAP I, II and III. As the Examiner is aware, according to the Written Description Guidelines, Applicant need not describe in detail that which would be well known to those of ordinary skill in the art.

Claim Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 84-103 under 35 U.S.C. §103(a) as allegedly being unpatentable over Delgado et al. (Journal of Bacteriology (2001) vol. 183, pages 4543-4555) in view of Korzheva et al. (Science (2000) Vol. 289, pages 619-625), Darst et al. (US 2002/0034808) and Woychik (Cell (February 2002) Vol. 108, pages 453-463).

The claims are directed to methods of identifying an agent that binds to and/or inhibits a bacterial RNAP homologous secondary channel amino acid sequence. The amended claims now recite that the bacterial RNAP homologous secondary channel amino acid sequence corresponds to, and is alignable with amino acid residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia Coli*. The claims are further directed to comparing the inhibition by an agent that binds to this specific target sequence with inhibition by an agent that binds to a bacterial RNAP derivative that includes at least one substitution, insertion, or deletion of amino acid residues in the target region or one that binds to human RNAP I, II or III.

The Examiner alleges that Delgado discloses methods relating to the target region referred to in the claims as the "bacterial RNAP homologous secondary channel amino acid sequence". Applicant strongly disagrees with the Examiner's allegations. For example, the "bacterial RNAP homologous secondary channel amino acid sequence" is defined in the specification as "a target region corresponding to, and alignable with residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia coli*..." (*see,* for e.g., paragraphs [0007], [0027], [0029] and [0090] of Applicant's published U.S. Application). In contrast, Delgado is completely devoid of any disclosure with respect to said "bacterial RNAP homologous secondary channel amino acid sequence." The mutant disclosed in Delgado and cited by the Examiner involves residue 931 of the β' subunit of RNAP from *Escherichia coli*. Residue 931 is not part of, or even near to, a target region corresponding to, and alignable with residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia coli*.

In fact, Delgado, et al. were aware that in "all likelihood" residues in addition to residue 931 of the β' subunit of RNAP were involved in binding microcin, and disclosed that they were in the process of systemically changing residues surrounding residue 931 in order to identify these additional residues. *See*, for example, last paragraph, at bottom of p. 4549 through top of p.

4550 of Delgado. The fact that they were continuing to look in the area surrounding residue 931 teaches away from the present invention as it would have led the skilled person in a direction which is not claimed.

Applicant has carried out extensive experimentation to systematically define the MccJ25 determinant within the RNAP secondary channel. In the absence of the disclosure of the present specification, it would not be reasonable for one of skill in art to allege that microcin binds to a target region corresponding to, and alignable with residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia coli*.

As described above, Applicant had already defined the "bacterial RNAP homologous secondary channel amino acid sequence" in the specification. However, in an effort to advance prosecution, the claims have been amended to specifically recite the target region corresponding to, and alignable with residues 736-747 and 779-781 of the β' subunit of RNAP from *Escherichia coli*. As disclosed in the specification, the present invention provides the target region of the β' subunit of RNAP from *Escherichia coli* by way of example only, and corresponding residues of the β' subunit of RNAP from other bacterial species are also within the scope of the claims (paragraphs [0031], [0090] and [0094] of Applicant's published U.S. Application).

The Examiner further alleges that "it would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of identifying an agent that binds to the bacterial RNAP secondary channel wherein agents ... are tested against MccJ25 as a control...". Again, Applicant's strongly disagree with the Examiner's allegations. At the time of the invention, there was no published disclosure, indeed not even published speculation, that MccJ25 functions through binding to the bacterial RNAP secondary channel specifically set forth in the

claims. Therefore, there would be no basis to use a method of identifying an agent that binds to the target region specifically set forth in the claims wherein agents are tested against MccJ25 as a control.

The secondary references fail make up for the deficiencies of the primary reference. Therefore, it is believed that all of the claims of the present invention are patentable over the cited references, either alone or in combination. Withdrawal of these rejections is therefore respectfully requested.

SUMMARY

Applicant has responded in full to the present Office Action. Favorable action thereon is respectfully solicited. If the Examiner should have any questions or concerns with respect to this matter, the Examiner is encouraged to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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